Relative Mitochondrial Toxicity of Tenofovir Alafenamide (TAF) vs. Tenofovir Disoproxil Fumarate (TDF)

Identifiers: NCT03251144

March 22, 2022

STUDY SCHEMA

HIV infected participants on stable antiretroviral therapy will be switched to newer antiretrovirals to evaluate the effect of these newer antiretrovirals on mitochondria.

Primary Objective(s) Primary Endpoint(s)	To assess in vivo the effects of TAF on mitochondrial health as assessed by several assays. Primary outcome will be cellular oxygen consumption (COC) and secondary outcomes the rest of measures of mitochondrial health as described in the study design.
Study Regimen/Intervention	**There are 3 scenarios based on the possible TAF-based regimens** **A) Scenario 1: TAF based regimen is Stribild** **Study Switch (Stribild→ Genvoya. Intervention: Genvoya** (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg; E/C/F/TAF) Emtricitabine 200 mg/tenofovir alafenamide 25 mg; E/C/F/TAF 1 tablet orally once daily. **Optional switch to expedite recruitment (see study design) (any other ART → Stribild): Intervention: Stribild®;** (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) 1 tablet orally once daily. **B) Scenario 2: TAF based regimen is ODEFSEY** **Study Switch (Complera (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Tablets) → ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide). Intervention: ODEFSEY** (25 mg rilpivirine + 200mg emtricitabine + 25mg tenofovir alafenamide fumarate) 1 tablet orally once daily. **C) Scenario 3: TAF based regimen is Descovy** **Study Switch (TRUVADA (emtricitabine/tenofovir disoproxil fumarate) + any other combination of antivirals --> Descovy (tenofovir alafenamide + emtricitabine) + any other combination of antivirals. Intervention: Descovy** (200 mg emtricitabine + 10 mg tenofovir alafenamide fumarate) 1 tablet orally once daily. **After any ART switch safety labs will be done within 2 months (will aim for 1 month post switch)**
Study Duration	There are a total of 3-5 study visits over a period **of up to 9 months**. **Visit 0:** (Optional) If not on Stribild, participant will switch from their current ART→ Stribild. Must stay on Stribild for 3 months before starting Visit 1. **Safety labs visit 0:** Follow up visit within 2 months after visit 0 (optional): Safety and early effects of Stribild (safety labs) will be assessed. **Visit 1:** Baseline visit: participant switched from TDF based regimen to TAF based regimen. A follow-up phone call will be made ~2 weeks after Entry. **Visit 2:** 2 month follow up visit: Safety and early effects of TAF based regimen on mitochondrial health will be assessed.

	Visit 3: 6 month follow up visit: differential in vivo effects of TAF based regimen on mitochondrial health will be assessed.
Study Population	30 participants will be enrolled Eligibilty criteria: • 18 years of age or older • HIV infected and on anti-retroviral therapy with suppressed viremia for at least 3 months (viral RNA <50 copies per ml) • On stable antiretroviral therapy for ≥ 6 months with TDF based regimens: 1) Stribild®; elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) OR 2) Complera (Emtricitabine 200 mg /Rilpivirine 25 mg/Tenofovir Disoproxil Fumarate 300 mg Tablets OR 3) Truvada (Emtricitabine 200 mg /Tenofovir Disoproxil Fumarate 300 mg Tablets • On stable antiretroviral therapy for ≥ 6 months with ***ANY OTHER than Stribild*** antiretroviral therapy and willing to switch to Stribild for at least 3 months. This optional switch (switch 1: old ART regimen to Stribild) will expedite recruitment and study completion (see study design). Once on 3 months of Stribild these participants would be eligible for switch from Stribild to Genvoya as described in the study design. • Adequate renal function determined by the Cockcroft-Gault formula for creatinine clearance (>60 mL/min/1.73 m2 • Able and willing to communicate in English • Able and willing to provide written consent

STUDY DESIGN

An open-label switch study will be conducted in virologically-suppressed, HIV-1 positive participants. The switch regiment will be: 1) Stribild®; elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) to Genvoya; elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg; E/C/F/TAF OR 2) Complera (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Tablets) to ODEFSEY (25 mg rilpivirine + 200mg emtricitabine + 25mg tenofovir alafenamide fumarate) OR 3) TRUVADA (emtricitabine/tenofovir disoproxil fumarate) + any other combination of antivirals to Descovy (200 mg emtricitabine + 10 mg tenofovir alafenamide fumarate).

Major eligibility criteria for study participants will be age > 18 years old, any CD4 T cell count, viral load <50 copies/ml or undetectable on E/C/F/TDF for the previous 3 months prior to the onset of study, adequate renal function determined by the Cockcroft-Gault formula for creatinine clearance and no evidence of acute hepatitis in the prior 30 days. Major exclusion criteria will be pregnancy and diseases or use of other drugs known to affect mitochondrial function. Subjects will have three clinical visits: one at baseline prior to the TDF to TAF switch, and follow up visits at 2 and 6 months after the switch. We will also include the option to switch ANY HIV-infected person who meets the inclusion criteria and not on an antiretroviral regimen other than Stribild [(Elvitegravir (ELV)/cobicistat CO)/emtricitabine (FTC)/tenofovir (TDF)] to switch to Stribild for 3 months. This will allow for future switch (after these 3 months) from Stribild to GENVOYA. This approach can expedite recruitment since we can switch HIV infected persons to Stribild and then do another switch from Stribild to GENVOYA as per study protocol. In addition given the known clinical benefits (less toxicity) of Stribild and Complera compared to older antiretrovirals (such as protease inhibitors)[Patient Prefer Adherence. 2015; 9: 1213–1218.; J Acquir Immune Defic Syndr. 2014 Mar 1; 65(3):e118-20; Lancet. 2012 Jun 30;379(9835):2439-48; J Acquir Immune Defic Syndr. 2014 Mar 1; 65(3):e121-4; AIDS. 2012;26:2315–2326; J Infect Dis. 2015;212(3):345–354] and the known clinical benefits of TAF compared to TDF (less bone and kidney toxicity) these ART switches are beneficial for the participant and they also allow us to study differential effects of TAF

vs TDF on mitochondria. The participants who will undergo any ART switch will have a clinic visit or a phone call 1-2 weeks after the ART switch to check for side effects/tolerability of the new regimen and all subjects will have a clinic visit with blood tests to check viral load and safety labs (complete metabolic panel and complete blood count) within 2 months after any switch. Then after informed consent has been obtained ART will be switched as per protocol.

During visits at baseline, month 2, 6, blood will be obtained for isolation of PBMC (measurement of mitochondrial function). This study design will account for confounders that may affect mitochondrial function among different subjects (given the intrinsic heterogeneity of mitochondria). All study participants will be recruited in outpatient clinics within UCLA. All HIV-1 infected participants will be recruited within the UCLA Center for AIDS Education and Research (UCLA CARE) Center which provides HIV care to over 1000 patients with HIV in Los Angeles and is regarded as one of the premier HIV care providers in the country. We anticipate recruiting 60 (30 HIV-1 infected and 30 uninfected) persons in total for all outlined experiments.

STUDY POPULATION

HIV-1-infected participants in the Los Angeles area will be recruited voluntarily through a UCLA IRB-approved protocol at UCLA Center for AIDS Research and Education (CARE).

Enrollment will be open to men and women from all socioeconomic strata and all race and ethnic groups. We anticipate enrolling 30 HIV-1 infected individuals in total.

4.1 Inclusion Criteria

- 18 years of age or older
- Cases: Chronically infected and on anti-retroviral therapy with suppressed viremia for at least 3 months (viral RNA <50 copies per ml)
- On stable antiretroviral therapy for >6 months with TDF based regimens: 1) Stribild®; elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) OR 2) Complera (Emtricitabine 200 mg /Rilpivirine 25 mg/Tenofovir Disoproxil Fumarate 300 mg Tablets OR 3) Truvada (Emtricitabine 200 mg /Tenofovir Disoproxil Fumarate 300 mg Tablet.
- On stable antiretroviral therapy for ≥ 6 months with ANY OTHER than Stribild antiretroviral therapy and willing to switch to Stribild for at least 3 months. This optional switch (switch 1: old ART regimen to Stribild) will expedite recruitment and study completion (see study design). Once on 3 months of Stribild these participants would be eligible for switch from Stribild to Genvoya as described in the study design.
- Adequate renal function determined by the Cockcroft-Gault formula for creatinine clearance (>60 mL/min/1.73 m2
- Able and willing to provide written consent

4.2 Exclusion Criteria

- History of taking medications that are known to have a major effect on mitochondrial function such as cyclosporine, mitochondrial antioxidants.
- History of mitochondrial disease
- Pregnancy
- Hepatitis; no evidence of acute hepatitis in the prior 30 days
- History of severe renal impairment (eGFR < 30 ml/min/1.73 m2)
- History of severe or recent cardiac event
- Current alcoholism or IV drug abuse
- Use of systemic immunomodulatory medications (e.g. steroids) within 4 weeks of enrollment
- Anemia precluding safe donation of blood (For men, anemia is typically defined as hemoglobin level of less than 13.5 gram/100 ml and in women as hemoglobin of less than 12.0 gram/100 ml).
- Use of any investigational products within 4 weeks of enrollment
- Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study or unable to comply with the study requirements. Such conditions

may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease.
- Subjects who are on medications that are strong inducers of CYP3A (as these may decrease the efficacy of Stribild or Genvoya). Examples include phenobarbital, phenytoin, carbamazepine, and rifampin.
- Subjects who are on medications that are cleared by CYP3A and that may be toxic with elevated drug levels (examples include Cisapride, ergotamine, Pimozide, Lurasidone, Lovastatin, and Simvastatin).

INTERVENTIONS

Regimen (dose, schedule, route, administration)

Scenario 1: TAF based regimen is **Genvoya**

Study Switch (Stribild→ Genvoya)
Intervention: Genvoya (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg; E/C/F/TAF) (1 tablet orally once daily for 6 months)

Scenario 2: TAF based regimen is ODEFSEY

Study Switch (Complera (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Tablets) ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide). Intervention: ODEFSEY (25 mg rilpivirine + 200mg emtricitabine + 25mg tenofovir alafenamide fumarate)

Scenario 3: TAF based regimen is Descovy

Study Switch (TRUVADA (emtricitabine/tenofovir disoproxil fumarate) + any other combination of antivirals --> Descovy (tenofovir alafenamide + emtricitabine) + any other combination of antivirals. Intervention: Descovy (200 mg emtricitabine + 10 mg tenofovir alafenamide fumarate)

Alternative switch to expedite recruitment (see study design) (any other ART → Stribild)
Intervention: Stribild® (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) 1 tablet orally once daily for 3 months.

Study Product Formulation and Preparation

- **Genvoya** (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg; E/C/F/TAF) 1 tablet, taken orally, daily (FDA approved).
- **Odefsey** (25 mg rilpivirine + 200mg emtricitabine + 25mg tenofovir alafenamide fumarate) 1 tablet, taken orally, daily (FDA approved).
- **Descovy** (200 mg emtricitabine + 10 mg tenofovir alafenamide fumarate) 1 tablet, taken orally, daily (FDA approved).
- **Stribild®;** (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; E/C/F/TDF) 1 tablet, taken orally, daily (FDA approved).

Study Product Supply and Accountability

The study medications Genvoya and Stribild will be provided to all study participants for the whole duration of the study by Gilead Biosciences as described in the agreement. The medications Odefsey and Descovy will be provided to all study participants in the setting of clinical care (switch by the primary care physician). The participants will remain on the appropriate antiretroviral therapy as per clinician's care/decision after the study and their ART outside the scope of the study will be covered

within the standard practices of clinical care.

Permitted Medications and Procedures

Any medications not listed as contraindicated in package insert

Prohibited Medications and Procedures

See package insert

SCHEDULE OF EVENTS

There are up to 5 study visits total (screening visit excluded). Participants not on Stribild before study enrollment will have 4 visits (screening visit excluded)); those already on Stribild will have 3 visits.

Day -90: switch from any other ART → Stribild. Must stay on Stribild for 3 months before starting Visit 1. Two weeks after this visit Dr Kelesidis or the study coordinator will contact the participant over the phone to see if the participant is handling the switch to Stribild okay.

Day -60 or up to -30: Follow up visit within 2 months after visit 0 (optional): Safety and early effects of Stribild (safety labs) will be assessed.

Day 0: Baseline visit: prescription given for Genvoya; begin switch from TDF based regimen to TAF based regimen.

Day 60 (2 month follow up visit): Safety follow-up and early (2 month post switch) differential in vivo effects of TAF based regimen on mitochondrial health will be assessed.

Day 180 (6 month follow up visit): Late (6 month post switch) differential in vivo effects of TAF based regimen on mitochondrial health will be assessed.

Blood draws will be done at Day -90, Day 0, Day 60, Day 180 for laboratory testing. Approximately 100mL will be collected at each visit, with no more than 400 mL total over the course of the study.

Screening

Medical records will be accessed and reviewed for:

- HIV status (e.g. CD4 count, viral load)
- Age
- Underlying condition and comorbidities
- Medications
- Labs e.g. creatinine to determine kidney and liver function

Switch to Stribild: switch from any other ART→Stribild. No additional blood draw.

Participants will undergo a blood draw (100mL) and then be given a prescription for TAF based regimen for 6 months (switch from TDF→TAF).

Entry/Day 0

Follow-up phone call

2 weeks after the Entry visit, a brief phone call from the PI or study coordinator will be made to participants to ensure they are adjusting to the switch okay. The following questions will be asked:

- Are you tolerating the new medication okay?
- Have you experienced any new symptoms since you started the new drug? (expected side effects from switching antivirals should have already been addressed at the initial study visit).
- Have you been taking all your pills?
- Do you have any questions we could answer for you?

If new symptoms appear, the participant will be instructed to schedule a visit with their care provider for standard evaluations.

Day 60 post-switch
Blood draw (100mL)

Day 180 post-switch
Blood draw (100mL)

Laboratory Evaluations
Mitochondrial function assays: The Seahorse method measures function through the COC (increased COC indicates reduced bioenergetic capacity and mitochondrial dysfunction).

Specimen Preparation, Handling and Shipping
Whole blood will be collected using standard phlebotomy and placed in standard heparin green top tubes. All tubes per participant will be placed in a biohazard bag and shipped at room temperature to Kelesidis Lab for further processing.

Ship to: Kelesidis Lab/Infectious Diseases
37-121 CHS 10833 Le Conte Avenue
Los Angeles CA 90095

Total Blood Volume
100 mL of blood will be collected during Day -90, Day 0, Day 60, and Day 180. No more than 400mL of blood will be collected for this study.

CARE Clinic will draw and collect blood to be sent to Kelesidis lab via courier. Kelesidis lab will handle all blood processing, including peripheral blood mononuclear cells (PBMCs),

Entry visit
- Fasting Lipid Profile

The following labs are to be done only if they have not been done within the last 3 months:
- CBC
- Complete metabolic panel
- HIV RNA PCR
- CMV antibody

Safety labs for Visit 2:
- HIV viral load
- T-cell subset
- CBC
- CMP
- Fasting Lipid Profile
-

Safety labs for Visit 3:
- CBC
- CMP
- Fasting lipid profile

100 ml of blood will be drawn per visit/phlebotomy. Out of this volume standard tubes for the standard clinical

labs (fasting lipid profile, complete metabolic panel, HIV RNA PCR, CMV antibody, T- cell subset) will be sent to the clinical laboratory as per standard clinic procedure. The rest of the whole blood will be placed in EDTA or green top tubes and will be shipped to Kelesidis lab via courier. It is expected that 1 million cells will be obtained per ml of whole blood and cells will be isolated and cryopreserved at Kelesidis lab.

ASSESSMENT OF SAFETY

Adverse Event Reporting and monitoring.

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.
The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, must be used for grading the adverse events in this protocol and is available on the DAIDS RSC Web site at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

The AEs/SAEs should immediately be reported to the Principal Investigator. All events should be reported to the local IRB if they are reportable per the local IRB's reporting criteria.
This study will be internally monitored biannually.

A Data Safety Monitoring Board is not needed for this single-center open-label Phase I clinical trial (safety related to mitochondrial toxicity) since the local investigator will have access to all data. Dr. Kelesidis will be available to provide direct evaluation of any clinically-related concerns that might arise during the study. The principal investigator will directly discuss with assigned independent persons appointed by Gilead any concerns for adverse events (mitochondrial toxicity) and make recommendations for continuing or stopping the study. It is important to emphasize that the clinical safety of the described antiretrovirals has already been established within large scale clinical trials. This exploratory study will investigate subtle molecular readouts of mitochondrial toxicity that have been associated with adverse clinical outcome in some settings (e.g. diabetes). However the exact clinical significance of the findings from this small exploratory study will need to be validated in further larger scale trials. Thus, given the nature and scope of this study we do not anticipate any major clinical side effects and stopping the study early if subtle effects of antiretrovirals on mitochondria are detected.

CLINICAL MANAGEMENT

Not Applicable.

Criteria for Discontinuation

The study may be discontinued at any time by the IRB, OHRP, or other government agencies when necessary to ensure the protection of research subjects.

Completion of study product(s)/intervention(s) as defined in the protocol

Criteria for Premature Study Discontinuation for an Individual Participant

- Participant repeatedly non-compliant with study product/intervention as prescribed
- Pregnancy or breastfeeding
- Request by participant to withdraw
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of study results
- Participants will be taken off of study in the event of virologic failure or in the event of grade 3 or higher adverse effects or intolerable grade 2 adverse effects

STATISTICAL CONSIDERATIONS

Study Endpoints

Primary Endpoint

Cellular oxygen consumption (COC): From all the measures of mitochondrial function **cellular oxygen consumption (COC)** will be considered the “gold standard” given it is a measure of the most important mitochondrial function (oxidative phosphorylation) that relates to clinical outcome. It is accepted that two independent measures of mitochondrial function can more reliably predict mitochondrial dysfunction compared to each one of the measures separately. Thus, given the uncertainty of what measure of mitochondrial function can best predict NRTI-induced mitochondrial toxicity, comparison of relative fold induction of mitochondrial dysfunction in PBMC compared to baseline measurement will be done.
Primary endpoint is continuous variables (measured in pmoles O2/min) and it will be compared between the 2 groups on different antiretrovirals (TAF based vs TDF based) cross sectionally using unpaired t-test. Changes in primary outcome within the same person will be determined by paired t-test (baseline and after switch). Statistical p value <0.05 will be considered statistically significant.